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Styrenated Phenols
Category Justification and Testing Rationale

CAS Nos.: 61788-44-1 and 68457-74-9
Rubber and Plastic Additives Panel of the
American Chemistry Council
Revised June 2003

List of Member Companies in the Rubber and Plastic Additives Panel

The Rubber and Plastic Additives Panel of the American Chemistry Council include the following member companies: Alcon Chemical Corporation; Bayer Polymers LLC; Ciba Specialty Chemicals Corporation; Crompton Corporation; Eliokem, Inc.; Flexsys America L.P.; The Goodyear Tire & Rubber Company; The Lubrizol Corporation; Noveon, Inc.; and R.T. Vanderbilt Company, Inc.

Executive Summary

The American Chemistry Council's Rubber and Plastic Additives Panel (RAPA), and its member companies, hereby submit a Test Plan and supporting documentation for the Styrenated Phenols category of chemicals under the Environmental Protection Agency's High Production Volume (HPV) Challenge Program. This submission constitutes a partial revision of documents previously submitted to the Program by the RAPA Panel. In the previous submission, dated December 18, 2001, the Styrenated Phenols were included in a category called "Hindered Phenols." In comments dated December 5, 2002, EPA noted that "the data provided by the sponsor support the category with respect to the physicochemical, environmental fate and ecotoxicological properties of these substances; the health endpoints are less well supported." Comments received from Environmental Defense (dated May 23, 2002) also raised concerns about the "Hindered Phenols" category. On reevaluation, the RAPA Panel concluded that, based on existing data, the comments raised useful points to be addressed in revised materials. Accordingly, revised Test Plans and Robust Summaries for the eight chemicals that comprised the former "Hindered Phenols" category will be submitted as two categories (Styrenated Phenols and Bridged Alkyl Phenols) and two stand-alone chemicals (CAS numbers 68610-51-5 and 27676-62-6). The Test Plan for Styrenated Phenols follows.

Styrenated phenols are non-staining, non-discoloring, non-migratory additives for natural rubber, synthetic rubber, adhesives, plastics, textile fibers, cable coatings, flooring, and coated paper as well as natural and synthetic oils. Their sole purpose is to prevent or greatly delay the deterioration caused by air oxidation. The styrenated phenols are very cost-effective and efficient antioxidants. Usage levels for most applications are typically within the range of 0.5 to 2%.

In consideration of animal welfare concerns to minimize the use of animals in the testing of chemicals, the Panel has conducted an extensive literature search for all available data,

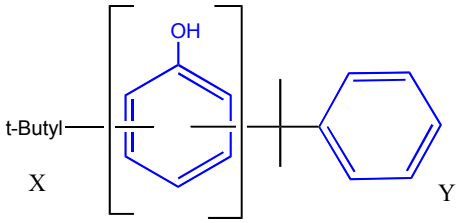
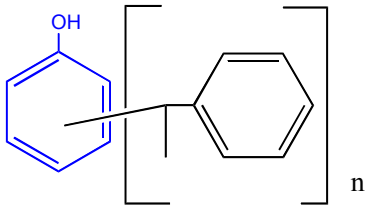
published and unpublished. It has also performed an analysis of the adequacy of the existing data. Further, it developed a scientifically supportable category of related chemicals and used structure-activity relationship information to meet certain data requirements.

Styrenated Phenols Category

As defined by EPA under the HPV Program, a chemical category is "a group of chemicals whose physicochemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity." The similarities should be based on a common functional group, common precursors or breakdown products (resulting in structurally similar chemicals) and an incremental and constant change across the category. The goal of developing a chemical category is to use interpolation and/or extrapolation to assess chemicals rather than conducting additional testing with specific consideration of animal welfare concerns to minimize the use of animals in the testing of chemicals.

Relying on several factors specified in EPA's guidance document on "Development of Chemical Categories in the HPV Challenge Program,"[1] in which use of chemical categories is encouraged, the following related chemicals constitute a chemical category.

Structural Similarity: The styrenated phenols category includes two substances in which a phenol has at least one substitution of alpha-methyl styrene on the aromatic ring. Styrenated phenol has multiple methyl styrly groups on the phenol ring. Isobutylated methylstyrenated phenol, in addition to the methyl styrly groups may also have one or two t-butyl substitutions.

isobutylenated methylstyrenated phenol (68457-74-9)	***styrenated phenol (61788-44-1)***
 X = 0, 1 or 2 Y = 1, 2 or 3	 n = 1, 2 or 3

Similarity of Physiochemical Properties. Both substances are liquids at room temperature. The vapor pressure of the substances is low. Water solubility is limited and partition coefficients are high.

[1] US EPA, Office of Pollution Prevention and Toxics. Development of Chemical Categories, Chemical Right-to-Know Initiative. http://www.epa.gov/opptintr/chemrtk/categuid.htm.

Fate and Transport Characteristics. Experimental data show that the styrenated phenols are not readily biodegradable. Hydrolysis data are not available because of low water solubility of the substances. Model derived photodegradation for styrenated phenol indicates that rapid photodegradation is expected for this group. Fugacity modeling shows that partitioning would be to water and soil.

Toxicological Similarity. Review of existing published and unpublished test data for the styrenated phenols shows that the toxicity between the two substances in this category would be expected to be similar.

> **Aquatic Toxicology**. One LC50 study in fish was available for this endpoint.
>
> **Mammalian Toxicology - Acute.** Acute oral and dermal toxicity data are available for both substances in the group and show that they are not acutely toxic.
>
> **Mammalian Toxicology - Genotoxicity.** Gene mutation assays in bacterial systems are available for both members of this category and an *in vivo* assay evaluating chromosome damage is available for isobutylenated methylstyrenated phenol. All mutagenicity tests, except one, were negative. The category has been adequately tested for mutagenicity for the purposes of the HPV Program, and no additional testing is proposed.
>
> **Mammalian Toxicology – Repeated Dose Toxicity**. A 12-week repeated dose toxicity study is available with styrenated phenol. Sufficient data are available to characterize the repeated dose toxicity of the styrenated phenols for the purposes of the HPV Program.
>
> **Mammalian Toxicology - Reproductive and Developmental Toxicity.** No data available.

Conclusion. The styrenated phenols meet the EPA definition of a chemical category. It consists of two substances in which the phenol has at least one substitution of alpha-methyl styrene on the aromatic ring. Isobutylated methylstyrenated phenol, in addition to the methyl styrly groups may also have one or two t-butyl substitutions. Because of the limited ecotoxicity data, acute toxicity testing in fish, Daphnia and algae are proposed. No data are available on reproductive or developmental toxicity. A reproduction/developmental toxicity screening test is proposed to evaluate reproduction and developmental toxicity for this category. Styrenated phenol is proposed as the test substance.

Introduction

A provision for the use of structure activity relationships (SAR) to reduce testing needs is included under the EPA HPV Program. Specifically, categories may be formed based on structural similarity, through analogy, or through a combination of category and analogy for use with single chemicals. The benefits of using a category approach are numerous. They include the accelerated release of hazard information to the public (category analysis and testing are proposed to be initiated within the first two years of the HPV Program); a reduction in the number of animals used for testing; and an economic savings as a result of a reduced testing program.

Two substances form the styrenated phenols category:

styrenated phenol (61788-44-1)
isobutylenated methylstyrenated phenol (68457-74-9)

The development of this category follows current EPA guidelines.

Background Information: Manufacturing and Commercial Applications

Manufacturing

A typical manufacturing process for a styrenated phenol antioxidant uses a substituted cresol raw material for the phenolic ring portion of the molecule, and an aldehyde raw material for the bridging or connecting group. The batch reaction takes place in an alcoholic solvent and utilizes an acid catalyst. When the reaction is complete, the batch is quenched with water and decanted. Purification steps may include additional water washes/decants before the product is slurried with a hydrocarbon solvent, vacuum filtered, washed with additional solvent, centrifuged and dried.

Commercial Applications

Styrenated phenols are non-staining, non-discoloring, non-migratory additives for natural rubber, synthetic rubber, adhesives, plastics, textile fibers, cable coatings, flooring, and coated paper, as well as natural and synthetic oils. Their sole purpose is to prevent or greatly delay the deterioration caused by air oxidation. Using a styrenated phenol antioxidant greatly extends the useful life of a transparent, translucent, white or light-colored article by preventing the formation of surface cracks, brittleness and yellowing. In oils, a styrenated phenol antioxidant functions as a stabilizer. It extends the useful life of the lubricating fluid by slowing the natural breakdown process and limiting the buildup of tars and residues. The overall mechanism is similar to that of the antioxidant vitamins A and E in the human body – styrenated phenol antioxidants serve as free-radical scavengers.

The styrenated phenols are very cost-effective and efficient antioxidants. Usage levels for most applications are typically within the range of 0.5 to 2%.

Due to its low toxicity styrenated phenol is cleared for use as antioxidants by the Food and Drug Administration (FDA) for two food-contact applications as an Indirect Food Additive:

175.105 Components of Adhesives
177.2600 Rubber Articles – Antioxidants

Shipping/Distribution
Styrenated phenol antioxidants are manufactured in North America, Europe and Asia. They are shipped worldwide for use at manufacturing sites engaged in the production of rubber and plastic articles and mechanical goods, food containers and food handling equipment, industrial oils and lubricants, synthetic fabrics and specialized papers.

Worker/Consumer Exposure
The rubber and plastics additives industry has a long safety record and sophisticated industrial users handle these materials. Exposure of workers handling styrenated phenol antioxidants is likely to be greater in the area of material packaging rather than from chemical manufacturing. These materials are liquids. Mechanized materials handling systems of the large industrial users help keep exposures to minimum levels. However, during material packout at the manufacturing site and, to a somewhat lesser degree during weigh-up activities at the customer site, there is a potential for skin and inhalation exposure.

Sales of the styrenated phenol antioxidants are to industrial users. There are no consumer uses for these materials as manufactured, so there are no known direct-to-consumer sales. Only very small amounts are used in the manufacture of rubber and plastics or as oil additives, and the materials themselves become bound in the polymer matrix during the rubber and plastic curing process. Consumer exposure to the styrenated phenol antioxidants is judged to be minimal. Should exposure occur, the most likely route would be skin contact from rubber and plastic articles, or from skin contact with oils.

Development of the Styrenated Phenols Category

EPA has described a stepwise process for developing categories. These steps include:
- Grouping a series of like chemicals, including the definition of criteria for the group.
- Gathering data on physicochemical properties, environmental fate and effects, and health effects for each member of the category.
- Evaluating the data for adequacy.
- Constructing a matrix of available and unavailable data.
- Determining whether there is a correlation among category members and data gathered.

Definition of the Styrenated phenols Category

As defined by EPA under the HPV Program, a chemical category is "a group of chemicals whose physicochemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity." The similarities should be based on a common functional group, common precursors or breakdown products (resulting in structurally similar chemicals) and an incremental and constant change across the category. The goal of developing a chemical category is to use interpolation and/or extrapolation to assess chemicals rather than conducting additional unnecessary testing.

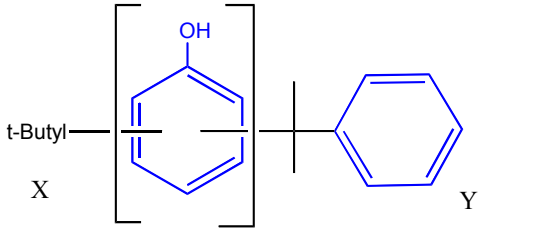
The substances to be included in this styrenated phenols category are:

Styrenated phenols

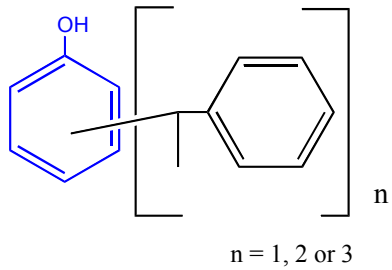
Name	CAS No.
isobutylenated methylstyrenated phenol	68457-74-9
styrenated phenol	61788-44-1

The styrenated phenols category consists of two substances in which a phenol (hydroxybenzene) has at least one substitution of alpha-methyl styrene on the aromatic ring. Styrenated phenol has multiple methyl styrly groups on the hydroxybenzene ring. Isobutylated methylstyrenated phenol, in addition to one or more methyl styrly groups, may also have one or two t-butyl substitutions.

Isobutylenated methylstyrenated phenol (68457-74-9) is hydroxybenzene with multiple aliphatic and/or aromatic groups on the aromatic ring.



Styrenated phenol (61788-44-1) has multiple aromatic styryl groups on the hydroxybenzene.



Matrix of SIDS Endpoints

In order to construct a matrix of SIDS endpoints for the styrenated phenols category, the data on physicochemical properties, environmental fate and effects, and health effects for each member of the category must be collected and evaluated for adequacy. The results are summarized in Table 1 and 2.

Correlation within the Styrenated Phenols Category

Physicochemical Properties: Both substances are viscous liquids at room temperature. The vapor pressure of these substances is low. Water solubility is limited and partition coefficients are high. All of the physicochemical data are experimentally determined except for the vapor pressure of styrenated phenol for which a value was calculated.

Environmental Fate: Experimental data show that the styrenated phenols are not readily biodegradable. Hydrolysis data are not available because of low water solubility of the substances. Model derived photodegradation for styrenated phenol indicates rapid photodegradation. Photodegradation for isobutylenated methylstyrenated phenol cannot be determined by modeling, but it would be expected that it would be similar to styrenated phenol. For styrenated phenol, fugacity modeling showed that it would partition primarily into water and soil. This can be extrapolated to isobutylenated methylstyrenated phenol. It is concluded that there are adequate data to evaluate the environmental fate of this group of styrenated phenols for the purposes of the HPV Program.

Ecotoxicity: The HPV Challenge Program requires acute tests in fish, invertebrates, and algae. The ecotoxicity data available for this category is a LD50 in fish where no toxicity was observed and the test was not conducted to the limit of solubility. To fulfill this data requirement, it is proposed that ecotoxicity testing be done with styrenated phenol as a representative compound for the group. Proposed tests include acute toxicity in fish, Daphnia and algae.

Correlation of Health Effects

Acute Mammalian Toxicity

Acute oral and dermal toxicity data are available for both substances in this category. The acute toxicity of these substances is low. While the acute toxicity tests with styrenated phenol are not to current guidelines, the tests with isobutylenated methylstyrenated phenol were conducted according to recent guidelines and under GLP. They support the conclusion that the acute mammalian toxicity of this group is low. No additional testing is necessary for the purposes of the HPV Program.

Genotoxicity

Genotoxicity test indicate that the styrenated phenols do not have potential to cause mutations.

Bacterial Gene Mutation Assays. Bacterial gene mutations assays have been conducted with both substances in the category. Assays were done with and without metabolic activation and were negative.

Chromosome Aberration Studies. A chromosome aberration study *in vivo* has been conducted with isobutylenated methylstyrenated phenol and was negative. It would not be expected that styrenated phenol would give different results than isobutylenated methylstyrenated phenol.

Other mutagenicity tests. An *in vitro* gene mutation assay with Mouse Lymphoma cells is available for isobutylenated methylstyrenated phenol and was negative. The only positive genotoxicity test was a bacterial DNA damage test with styrenated phenol.

Based on the available data, it is concluded that this endpoint has been adequately evaluated and no additional testing is needed for the purposes of the HPV Program.

Repeated Dose Toxicity

A 12-week feeding study has been conducted with styrenated phenol. In the study the thyroid was identified as a target organ and a NOAEL (50 mg/kg/day) and LOAEL (158 mg/kg/day) established. It is concluded that this study is sufficient to evaluate the repeated dose toxicity for the styrenated phenols for purposes of the HPV Program.

Reproductive and Developmental Toxicity

There are no data available on the reproduction or developmental toxicity of the styrenated phenols. To evaluate this endpoint, it is proposed that the Reproductive/Developmental Toxicity Screening Test (OECD Guideline 421) be conducted with styrenated phenol.

Conclusion

The styrenated phenols meet the EPA definition of a chemical category. It consists of two substances in which a phenol has one or more substitutions of alpha-methyl styrene on the aromatic ring. Styrenated phenol has multiple methyl styrly groups on the hydroxybenzene ring. Isobutylated methylstyrenated phenol, in addition to the methyl styrly groups, may also have one or two t-butyl substitutions.

The Test Plan for the styrenated phenols is summarized in Table 2. The test plan was developed giving careful consideration to the number of animals that would be required for any tests that are not available for the category and whether these additional tests would

provide useful and relevant information. To provide additional ecotoxicity data, acute toxicity tests in fish, Daphnia and algae are proposed. Reproduction/developmental toxicity screening test (OECD 421) with styrenated phenol is proposed to evaluate the reproductive and developmental endpoint.

Table 1.
Matrix of Available and Adequate Data for the Styrenated Phenols Category

	isobutylenated methylstyrenated phenol (68457-74-9)	**styrenated phenol (61788-44-1)**
Physicochemical Properties		
Molecular Weight	386 (average)	330 (average)
Melting Point		<0 ^{0}C
Boiling Point	350 ^{0}C	230 ^{0}C
Vapor Pressure	0.0018 mm Hg at 25 ^{0}C	0.102 mm Hg at 25 ^{0}C (calculated)
Water Solubility	0.0287 – 0.375 mg/L at 30 ^{0}C pH 7.9 - 8	59 mg/L at 20 ^{0}C pH 5.6 – 5.9
Partition Coefficient	>6.2	>4
Environmental Fate		
Hydrolysis	cbd	NDA
Photodegradation	cbd (EPIWIN)	$T_{1/2}$ = 2.2 hr (EPIWIN)
Biodegradation	Aerobic degradation <1% after 29 days	Aerobic degradation 7% after 28 days
Environmental Transport	cbd (EPIWIN)	Primarily water and soil. (Level III Fugacity Model)
Ecotoxicity		
Acute Fish 96-hr LC50	NDA	3.2 mg/L
Acute Invertebrate 48-hr EC50	NDA	NDA
Algal Growth inhibition EC50	NDA	NDA

cbd - cannot be determined due to low solubility
cbd (EPIWIN) - cannot be determined by modeling
NDA - No data available

Table 1. (continued)
Matrix of Available and Adequate Data for the Styrenated Phenols Category

	phenol, isobutylenated methylstyrenated (68457-74-9)	**phenol, styrenated (61788-44-1)**
Acute Toxicity		
Oral	> 2000 mg/kg	3700 mg/kg
Dermal	> 2000 mg/kg	> 5010 mg/kg
Genotoxicity		
Bacterial Gene Mutation		
S. typhimurium	negative	negative
Chromosomal Aberration		
In vitro	NDA	NDA
In vivo	negative	NDA
Others		
Mouse Lymphoma Forward Mutation	negative	
DNA Damage in Pol A+/A-		positive
S. cervisiae		negative
Repeated Dose Toxicity		
Subchronic	NDA	12-Week feeding study in rats - Growth was retarded and liver wt relative to bw. were higher than controls; minimal focal thyroid hyperplasia. NOAEL = 50 mg/kg/day LOAEL = 158 mg/kg/day
Reproductive and Developmental Toxicity		
Reproductive	NDA	NDA
Developmental	NDA	NDA

cbd - cannot be determined due to low solubility
cbd (EPIWIN) - cannot be determined by modeling
NDA - No data available

Table 2.
Test Plan for the Styrenated Phenol Category

	phenol, isobutylenated methylstyrenated (68457-74-9)	phenol, styrenated (61788-44-1)
Physicochemical Properties		
Boiling Point	NA	A
Melting Point	A	A
Vapor Pressure	A	C
Water Solubility	A	A
Partition Coefficient	A	A
Environmental Fate		
Hydrolysis	NA	NA
Photodegradation	R	C
Biodegradation	A	A
Environmental Transport	R	C
Ecotoxicity		
Acute Fish 96-hr LC50	NDA	Testing proposed
Acute Invertebrate 48-hr EC50	NDA	Testing proposed
Algal Growth inhibition EC50	NDA	Testing proposed
Acute Toxicity		
Oral	A	A
Dermal	A	A
Genotoxicity		
Bacterial Gene Mutation	A	A
Chromosomal Aberration		
In vitro	NDA	NDA
In vivo	A	R
Others		
Mouse Lymphoma Forward Mutation	A	
DNA Damage in Pol		A
S. cervisiae		A
Repeated Dose Toxicity		
Subchronic	R	A
Reproductive and Developmental Toxicity		
Reproduction/developmental toxicity	NDA	Testing proposed

A - Endpoint requirement fulfilled with adequate existing data
C - Endpoint requirement fulfilled based on calculated data
NA - Not applicable due to physical/chemical properties
NDA- No data available
R - Endpoint requirement fulfilled using category approach, SAR